R E M A R K S

This communication is responsive to the Office Action mailed in the above-captioned application on October 21, 1994.

Claims 1-15 are presented for examination.

Reconsideration and reexamination of the application in light of the remarks herein set forth is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Applicant respectfully traverses the rejection on grounds that specification is not enabling for the invention of claims 1-15.

Applicant notes that the claims are rejected *en mass*, as it were, for reasons that span seven pages of the Office Action. The action appears to set out several different reasons for rejection, but individual arguments appear to be interspersed. Applicant has attempted to organize the reasons for rejection into distinct arguments, which are addressed one-by-one in the following remarks. Hopefully, applicant has grasped each of the issues raised by the examiner. If any point has not been addressed, applicant requests the examiner's forbearance and further explanation identifying any point that has been overlooked.

Preliminary to the discussion of the individual grounds for rejection, applicant reiterates the following point regarding enablement, set out in the previous communication in this application.

The starting point for rejection on enablement grounds long has been taken from the decision of the CCPA in *In re Marzocchi*:

> As a matter of Patent Office practice, then, a specification disclosure which

> contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as in compliance with the enablement requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exit, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.[1]

It is submitted respectfully that several aspects of the present rejection do not set forth the reasons required by *Marzocchi* for rejection on enablement grounds, and are improper for this and other reasons as discussed below.

1. The examiner maintains that it will require undue experimentation to make and use the claimed invention unless the plasmids WAPpC1 and WAPpC2 are made available to the public by deposit.

In this regard, the examiner again maintains that reference in the specification to an individual source of DNA, which by assertion and by additional evidence has been shown to be well known and readily available, indicates that the DNA must be deposited to insure public availability.

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[1] Original emphasis italicized, other emphasis added. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971).

Applicant states in the application that DNA for practicing the invention may be obtained from a variety of sources. Applicant has reiterated this point in the responses. Applicant has documented the availability of DNAs identical to those used to construct the plasmids subject to the requirement for deposit. And, applicant has shown that constructs made with other DNAs do, in fact, work in the claimed invention, as disclosed.

Thus, applicant has shown that (1) DNAs for making WAP/protein C constructs of the invention are well known and readily available and (2) that constructs made from such starting materials can be used to practice the claimed invention.

Accordingly, applicant maintains that the deposit requirement should be withdrawn.

2. The examiner maintains that enablement is limited to transgenic mice and transgenic pigs.

In this regard the examiner alleges that the art the of protein expression in transgenic animals is unpredictable, and enablement therefore is limited to the specific embodiments actually reduced to practice.

Applicant respectfully points out that predictability in the art as whole is germane only as it relate to the claimed invention. As to the presently claimed invention, evidence provided by applicant clearly is the most pertinent information regarding predictability. Applicant has shown that protein C is expressed in the mammary glands of mice and pigs, using complementary DNA encoding protein human protein C and genomic DNA encoding human protein C, using several promoters including long and short mouse WAP promoters and a sheep β-lactoglobulin promoter, and several different

promoter-DNA constructs comprising these promoters and protein C-encoding DNAs. It is in the context of these multiple demonstrations of protein C expression targeted to mammary glands that "predictability" and "undue experimentation" must be judged.

Applicant submits that, regardless of the predictability of the art for other genes in other tissues in other mammals, the evidence provided by applicant shows that protein C generally may be expressed in mammary glands of transgenic non-human mammals. This, together with empirical results related specifically to the long WAP promoter of the presently claimed invention, show that enablement in the specification is commensurate in scope with the present claims.

Applicant notes furthermore that protein C has been expressed with each of the promoters that have been employed, with each of the protein C-encoding DNAs that have been employed, with each of the promoter-protein C constructs that have been employed, and in each of the animals that have been employed. The long WAP promoter of the claimed invention has worked in each case it has employed, as well.

The rejection thus not only does not advance a valid *prima facie* basis for rejection, it does not address the clear evidence of record that demonstrates actual reduction to practice that rebuts any *prima facie* case that might have been advanced. Different DNAs constructed from different source material have been employed successfully to express protein C in evolutionarily distant mammals. There is no reason to believe that the DNAs are unique or the animals special in any way not disclosed in the present application. Any concern regarding "uniqueness" of the animals must yield to the

evidence, which firmly provides an expectation that the claimed invention generally will operate in other lactating mammals.

In sum, the evidence indicates that protein C expression in accordance with the claimed invention can be achieved using a variety of mammals, and there is no reason of record to believe that another mammal somehow lies outside the scope of enablement simply because applicant has not reduced the invention to practice in that animal. Accordingly, applicant submits that this ground of rejection should be withdrawn.

3. The examiner also maintains that enablement is limited to:

(a) the *Eco*R1 protein C-encoding DNA fragment cloned in the *Eco*R1 site of WAPpC1 and WAPpC2 linked to the mouse whey acidic protein promoter, or

(b) the protein C-encoding human genomic DNA fragment beginning 21 basepairs 5' of the initiation codon and ending at the *Nhe*I site 3' of the termination codon operatively linked to the *Sau*3A-*Kpn*1 fragment of the mouse whey acidic protein promoter.

The rejection in this regard apparently is focused on the allegations that: (1) the examiner cannot determine if other DNAs are the same as these DNAs, or would work in transgenic animals the same as these DNAs; (2) that the specification does not define and does not enable the phrase "having protein C activity;" and (3) that the specification guidance would not enable those of skill to produce protein C as broadly as claimed without undue experimentation.

Applicant notes and reiterates the points set out above regarding the deposit requirement and the assertion that enablement is limited to mice and pigs.

Applicant respectfully points out that the claimed invention relates to the expression of protein C in milk of transgenic mammals using a particular class of DNAs. Predictability in the art as whole is germane only as it relates to this claimed invention. Applicant has shown that protein C can be expressed in milk of mice and pigs, that it can be expressed using complementary DNA encoding protein human protein C and genomic DNA encoding human protein C, and that it can be expressed using several promoters including a long and a short mouse WAP promoter and a sheep β-lactoglobulin promoter. It is in the context of the multiple demonstrations of protein C expression in transgenic animals that "predictability" and "undue experimentation" must be judged.

Applicant submits that, regardless of the predictability of the art for other genes in other tissues and other mammals, the evidence shows that protein C can be expressed using each of the protein C-encoding DNAs that have been employed, each of the promoter-protein C constructs that have been employed, and in each of the animals that have been employed.

The examiner's point that integration is random and may inactivate injected DNA is true of <u>all</u> DNAs, not just those that contain the WAP promoter and encode protein C. The phenomena is an inherent aspect of making transgenic animals by embryo injection. The fact, however, is irrelevant to enablement of the claimed invention, because (1) it is true of all DNAs and (2) applicant has provided several examples of reduction to practice.

Regarding integration, therefore, the rejection merely states a fact attendant to the production of every transgenic animal, no matter what DNA is employed. The fact is not a property of the DNAs of the illustrative examples. The fact, moreover, is well-recognized and never has prevented the production of transgenic animals. Thus, it cannot be said that those of skill would doubt the objective truth of the asserted enablement because DNAs of the claimed invention will integrate randomly in the host genome. This would be as true of any DNA as those of the claimed invention, and the assertion therefore amounts to a conclusion that those of skill doubt that any transgenic animals can be produced using a particular DNA, absent specific, actual reduction to practice. Applicant submits that this conclusion is not corrected and this basis for rejection should be withdrawn.

Furthermore, even if the reasons advanced in the rejection met the initial burden of the Patent Office, it is submitted that the evidence of record rebuts any *prima facie* case that might be fashioned in this regard. The facts are that different DNAs constructed from different source material have been employed successfully to express protein C. Each DNA and each type of animal that have been "tested" have proven amenable in this regard in accordance with this disclosure and the disclosure in the parent application. *A priori* concerns regarding "uniqueness" of the DNAs, however cogent, must yield to the clear evidence of record showing that the protein C generally can be expressed and, therefore, that the claimed long WAP-promoter DNAs will work as disclosed in the application.

As a final note in this regard, applicant respectfully points out that several documents submitted with regard to the requirement for deposit, as well as documents referenced in the application, referenced in previous responses and referenced in the office actions issued in this case, all demonstrate that protein C can be expressed using cloned genes in cultured cells *in vitro*. Thus, the evidence is absolutely incontrovertible that a variety of cloned genes, obtained from a variety of well known and readily available starting sources, can be used to express protein C. The venue of expression does not alter the inherent ability of the DNAs to express protein C, and there is absolutely no basis to assert that only a particular DNA that encodes protein C can be used to express protein C in transgenic animals.

Applicant also notes that the rejection links the scope of enablement to alleged indefiniteness in defining the "activity" of protein C recited in the claims. The rejection previously indicated that "[A]pplicant has not taught an assay method to determine DNA sequences which encode a protein having protein C activity." The rejection states that the "activity" will not be clear to those of skill and that the disclosed assays will not enable assays of mutant protein C activity.

Applicant believes that both statements are incorrect. The specification sets forth several well known protein C activity assays, such as those in EXAMPLES 7 and 8. Those of skill readily will appreciate how to use these assays to test protein C for activity, from transgenic milk or any other source. Indeed, the literature provided in the previous response shows that those of skill routinely measure activity of protein C and protein C variants.

Applicants therefore note that the Patent Office itself recommends that applications not belabor well known information.[2] The claimed invention relates to specific transgenic mammals which express protein C by a specific genus of DNAs. Methods for assaying protein C activity, *inter alia*, are well known and may be employed in the conventional manner in carrying out the invention. Several measures and assays for assessing protein C activity are set out in the disclosure. It would not require undue experimentation to use any of these assays to test protein C in milk of a transgenic animal. To the contrary, it would be routine for anyone making a transgenic animal that expresses protein C to use any of these assays. A person of skill would carry out such tests routinely, if only to determine that the animals produced active protein. There is no element of undue experimentation in carrying out such tests, however many different assays may be employed. Thus, it is respectfully submitted that the application is enabling for transgenic animals that express active protein C as claimed.

For the reasons set forth above, it is submitted that the present grounds for rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

It is respectfully submitted that the claims are clear and definite.

As set out in the previous response, the meaning of "substantially" and "variant thereof" is set forth with

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[2] *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

respect to the 5' 4.2kb WAP promoter fragment on page 20 line 2 through page 21 line 2, for instance.

In addition, substantially similar genomic protein C fragments are defined on page 18 lines 5-24, for instance. Applicant submits that these passages reasonably will inform those of skill in the art of the metes and bounds of the claimed invention to the maximum extent permitted by the art.

The rejection has been maintained from the previous action, on grounds that the foregoing passages do not define the terms at issue. No explanation is provided for this conclusion as it relates to the above-indicated disclosure. Applicant respectfully requests an explanation for the conclusion regarding the indicated, defining passages, or withdrawal of the rejection.

FIRST REJECTION UNDER 35 U.S.C. §103

All of the claims, except claim 11, have been rejected for obviousness over Pittius *et al.* ("Pittius"), Grinnell *et al.* (1987) ("Grinnell'87"), Brinster *et al.* ("Brinster") Campbell *et al.* ("Campbell") and Clark *et al.* ("Clark"). The rejection is maintained from the previous action.

Briefly, Grinnell (1987) is cited as teaching the expression of human protein C in tissue culture cells. Pittius is cited for teaching the expression of human t-PA in the milk of a transgenic mouse using a mouse whey acidic protein gene. Brinster is cited for teaching that intron sequences enhance transgene expression in mice. Campbell is cited for teaching the sequence of a mouse whey acidic protein gene. Clark is cited for teaching that compounds of pharmaceutical interest can be produced in the milk of transgenic animals.

The rejection asserts that the claimed invention would have been obvious because "the ordinary artisan would be provided a reasonable expectation of success in producing protein C or any other protein of interest in the milk of a transgenic non-human mammal."[3] The rejection particularly alleges that this would be so "where the transgene is composed of the genomic sequence for protein C or a protein of interest operatively linked to the mouse whey acidic promoter."[4]

More specifically the rejection alleges that the "The 4.2kb Sau3A-Kpn1 fragment of the whey acidic promoter" recited in the claims would have been "[o]bvious over the smaller fragment taught by Pittius" on grounds that "[optimizing] expression would be within the scope of skills of the ordinary artisan."[5]

In addition, the rejection alleges that "[T]he specific genomic protein C DNA sequence would be a matter of choice on the part of the inventor [*sic*]."[6]

The rejection is traversed for the reasons set forth in the previous response, as augmented and summarized below.

I. THE CLAIMED INVENTION ACHIEVES "UNEXPECTED RESULTS" AND THEREFORE WOULD NOT HAVE BEEN OBVIOUS

The transgenic animals of the claimed invention have unexpected properties of improved expression of protein C in milk and greater tissue specificity of

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[3] Quoting from the previous action.

[4] Quoting from the previous action.

[5] Quoting from the previous action.

[6] Quoting from the previous action.

expression. As set forth in the disclosure in EXAMPLE 11, transgenic animals of the claimed invention express surprisingly more protein C in their milk than animals in which protein C expression is promoted by the 2.4 kb WAP promoter of the prior art.

As set forth on page 48, lines 11-15 and in Table 5 on page 49 of the present disclosure, for instance, protein C was expressed in the milk of animals of the claimed invention in concentrations between 140 and 4,000 micrograms per milliliter. These concentrations are much higher than the results previously achieved using the 2.4 kb short WAP promoter fragment and a cDNA encoding protein C. For instance, as stated on page 33, lines 26-28, the majority of mice produced by microinjection of WAPpC1 produced protein C in milk in concentrations ranging between 1 and 4 micrograms per milliliter.

Production of protein C in 30 to 1,000-fold higher concentrations than previously observed was entirely unexpected. There was no basis upon which those of ordinary skill in the art could have expected such high levels of expression. There is no basis to make a rejection for obviousness over these unexpected results.

The rejection does not properly address the claimed invention in this regard. The prior art does not suggest that transgenic animals containing the DNAs specifically recited in the claims would be any different from transgenic animals containing any other WAP/protein C-encoding DNAs. Whatever motivation might have been present, those of ordinary skill in the could not have had a reasonable expectation that the DNAs recited in the claimed invention would be better than any other DNAs for expressing protein C in the milk of transgenic animals.

That is, they could not have had a reasonable expectation of success in this regard.

The rejection asserts that the long WAP promoter of the claimed invention would have been obvious by mere "optimization" and the genomic protein C-encoding DNA or the claimed invention would have been obvious as a "choice."

With due respect, the prior art does not teach any long WAP promoter or specific genomic DNA to choose. In addition, "optimization" to increase expression of protein C in milk is merely the notion that those of ordinary skill might undertake experiments to try to improve expression of proteins in transgenic animals. There is nothing about "optimization" of this type that, *a priori*, can be seen to render obvious the specific DNAs and animals of the claimed invention. There was no motivation to make transgenic animals containing the particularly recited DNAs, there certainly was no reasonable expectation that transgenic animals containing the particularly recited DNAs would have produced better results than other DNAs, and there was no basis to expect that transgenic animals containing DNAs in accordance with the claimed invention would be dramatically better able to express active protein C than other DNAs of apparently similar functionality.

Therefore, it is respectfully submitted that the rejection is improper for failing to give proper weight to the unexpected results set out by applicant. Accordingly, it should be withdrawn.

II. THE REJECTION, IN ANY CASE, DOES NOT SET OUT A PROPER *PRIMA FACIE* CASE OF OBVIOUSNESS

In addition, applicant again maintains that the expression of active protein C in the milk of transgenic

animals in accordance with the claimed invention would not have been *prima facie* obvious to those of ordinary skill at the time the claimed invention was made.

Applicant has pointed out that protein C is a complex protein that undergoes a variety of unusual modifications. The prior art teaches that mammary epithelial cells are not a good choice for carrying out these modifications efficiently, including modifications necessary for protein C activity. Indeed, the prior art teaches away from the claimed invention rather than suggesting it. For this reason alone the rejection should be withdrawn, as discussed in detail in the previous response.

Pittius relates to t-PA, a relatively simple protein compared to protein C. t-PA is processed naturally in cells by proteolytic cleavage which produces an enzymatically active protein. Protein C is secreted in an inactive, zymogen form. The proteases that carry out the processing are not the same for the two proteins. Likewise, although both proteins are glycosylated, the patterns of glycosylation are very different and are carried out by different enzymes. Proper processing of t-PA in a cell does not indicate that protein C will be processed correctly, even for the same types of modification. Furthermore, protein C undergoes two additional covalent modifications which are not observed in t-PA at all. The first, ß-hydroxylation, is relatively rare in proteins. The second, gamma carboxylation, generally is rare in proteins but is characteristic in the vitamin K-dependent enzymes of the coagulation cascade.[7] Moreover, protein C must be gamma carboxylated to exhibit

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[7] Gamma carboxylation is not a glycosylation.

anti-coagulant activity. Gamma carboxylation is not found in t-PA. t-PA expression demonstrated by Pittius thus is not at all informative regarding the expression of active protein C in accordance with the claimed invention.

Furthermore, the prior art showed that cultured mammary epithelial cells do not efficiently gamma carboxylate protein C, and therefore provided the expectation that protein C, specifically, could not be produced efficiently in mammary cells and milk of transgenic animals. This fact overrides any teaching of Pittius, whatever that reference may teach, because the prior art shows that mammary epithelial cells do not efficiently carry out modifications that are necessary to protein C activity but irrelevant t-PA expression and activity.

In addition, the prior art taught that other cells and tissues would be better suited to expression of protein C. As pointed out in previous responses, Grinnel (1987) relates to protein C expression in kidney cells in culture, and other publications related that the best expression of protein C in culture occurred in kidney cells, not mammary epithelial cells.[8] Indeed, the worst results in terms of the rates of synthesis and secretion of active protein C were obtained in a mouse mammary epithelial cell line.

Similarly, studies of protein gamma-carboxylation in cells of whole organs showed that liver cells are most active in this regard. Thus, mammary gland epithelial cells had been shown to be inferior to other cells for actual

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[8] Work on the production of protein C in cell culture is reviewed in Grinnel (1990), submitted as document B2 in the I.D.S. submitted on December 31, 1992.

production of protein C and for carrying modifications necessary to protein C activity.

Indeed, judged by the objective criteria of Grinnel and co-workers in Yan (1989) and Grinnel (1990) kidney cells would have been the best choice for protein C production and mammary epithelial cells would have been the worst choice. Thus, where Pittius is irrelevant or at least greatly incomplete regarding expression of active protein C in transgenic milk, Grinnel (1987) points away from the claimed invention by highlighting the inadequacy of mammary epithelial cells in this very regard. This also shows that it would it would not have been obvious to express high levels of protein C in the milk of a transgenic animal, as disclosed and claimed in the present application.

The conclusion is further strengthened by other references discussed in the previous response. Including several additional papers of Grinnel and co-workers relating to the expression of protein C in cell culture, the results discussed in Berg (1991), Suttie (1986) and Oppenheimer *et al*. These references and the prior art as a whole all indicated that mammary epithelial cells, and thus mammary glands, do not express high levels of active protein C, and that other types of cells are considerably better suited to this end.

Accordingly, the prior art directed the skilled artisan to produce protein C in kidney or liver cells, and further directed the skilled artisan not to produce protein C in mammary cells. Even if it is maintained that the prior art provided a suggestion regarding the production of active protein C in a transgenic animal, therefore, it cannot be maintained that it would have been

obvious to express protein C in mammary epithelial cells for secretion into milk.

Moreover, it will be appreciated that the claimed invention does not relate simply to transgenic expression of protein C. Indeed, the claimed invention recites transgenic animals, among other things, that comprise specific DNAs for expression protein C in milk. The cited prior art does not relate at all to the specific DNAs of the claimed invention, except obliquely, as the outcome of an optimization, as discussed above.

For all of the foregoing reasons it is respectfully submitted that the rejection of claims 1-10 and 12-15 for obviousness be withdrawn.

SECOND REJECTION UNDER 35 U.S.C. §103

Claim 11 has been rejected for obviousness over Colpan *et al.* ("Colpan") in view of Hogan *et al.* ("Hogan"). Colpan is cited for teaching purification of DNA by anion exchange HPLC. Hogan is cited for teaching that DNA for making transgenics should be free of contaminants that would deleteriously affect normal embryo development.

The rejection assert that "New uses for known methods do not necessarily overcome the art in the absence of unexpected results." On this basis the rejection requires "[S]ide by side comparisons" which show unexpected results to prove that the invention would not have been obvious. The rejection is traversed for the reasons set forth below.

For the reasons set out in the previous response, repeated below, it is respectfully submitted that the rejection does not set out a proper case of *prima facie* obviousness. It implies that purification of DNA

according to Colpan was a "known method" and it asserts that Hogan teaches the importance of removing deleterious contaminants from DNA used to make transgenic mice. The rejection does not set out a reasoned argument showing that a person of ordinary skill would have been motivated to use the Colpan method to make transgenic DNA. The rejection does not set out a reasoned argument to establish that a reasonable expectation of success would have attended such an endeavor. And the rejection does not address the fact that Hogan, which was published after Colpan, only teaches other methods for purifying DNA to make transgenic mice.

In fact, the references cited by the examiner indicate that the claimed invention would NOT have been obvious. As noted in the rejection, Hogan teaches that deleterious impurities most be removed from DNA for making transgenic animals. However, Hogan also teaches what it considers the best purification methods for this purpose. Hogan, written in view of Colpan, does not teach or suggest that a method according to Colpan would be useful in this regard. Hogan directs those of ordinary skill exclusively to methods other than the method in Colpan.

Hogan is an authoritative laboratory manual of reliable techniques for making transgenic mice. It indicates that those of ordinary skill in the art would not have used a method according to Colpan. In this regard, Hogan teaches against the claimed invention.

Colpan does not remedy this deficiency in Hogan as a reference under Section 103. Colpan neither teaches nor suggests using DNA purified by anion exchange HPLC to make transgenic animals.

It is respectfully suggested that all purification methods suffer from imperfections. Those of ordinary

skill in the art would not resort to the method in Colpan, as opposed to those taught by Hogan specifically for purifying DNA to make transgenic animals, without a motivation to do so. New methods pose risks. Colpan at most is an invitation to try anion exchange HPLC purified DNA in making transgenic animals. Nothing in the prior art suggested that the method would be successful in this regard or superior to the methods in Hogan.

The rejection does not address either point. It does not establish that those of ordinary skill in the art would have been motivated to forego the reliable methods in Hogan to use an untried method as set forth in Colpan. Furthermore, the rejection does not establish that they would have had a reasonable expectation that anion exchange HPLC would be as effective at removing deleterious contaminants as the methods in Hogan, whatever the asserted purity by weight or mass of DNA prepared by the method.

Finally, it should be noted that claim 11 is directed to making transgenic animals using the particular WAP promoter and protein C-encoding DNAs discussed above. The rejection does not address this aspect of the claimed invention, which distinguishes the claimed method over Colpan and Hogan, notwithstanding the foregoing remarks.

Accordingly, for the reasons set forth above, it is respectfully submitted that the rejection is improper and should be withdrawn.

In view of the foregoing amendments and remarks it is believed that the application now is in condition for allowance, and favorable disposition of the application is solicited.

A FINAL NOTE

The documentation referred to herein was submitted in the previous response. The documents reflect applicants' assessment that those of skill in the art will appreciate the veracity of the foregoing remarks concerning the level of skill, routine techniques and basic principles of science in this art, *inter alia*. It is believed that an examiner will be in the same position as those of skill in the art, in this respect, as well. Should the examiner desire additional documentation in this regard, it will be provided upon request.

Applicant specifically reserves the right, however, to submit additional documentation supporting the foregoing remarks if applicable grounds of rejection are reinstated in future Office Actions. Applicant particularly reserves the right to make of record additional documentation to complete the record in this regard in the event rejections are appealed to the Patent and Trademark Office Board of Appeals and Patent Interferences.

April 21, 1995
Date

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